This Month in *The Journal*

Sara B. Cullinan[1]

ABCs of Coloboma

Wang et al., page 40

Nearly 10% of all childhood blindness is caused by ocular coloboma, the abnormal or incomplete fusion of the optic fissure. Proper eye development requires the careful spatiotemporal orchestration of numerous transcription factors and signaling molecules. As such, there are many possible missteps that can occur prior to the fusion event. Although much research has been done that aims at identifying the genetic underpinnings of coloboma, the cause is known for only about half of the diagnosed cases. In this issue, Wang et al. show that mutations in *ABCB6* cause ocular coloboma. In addition to finding patient-derived mutations, experiments in zebrafish show that decreased *Abcb6* expression results in developmental delay and coloboma-like phenotypes. ABCB6 is a member of the ABC family of transporters; it is thought to function in iron metabolism and/or homeostasis. In addition to providing insight into the genetic and molecular underpinnings of coloboma, this finding lends further support to the idea that dysregulation of metal ions underlies ocular disorders. The ability to screen zebrafish for a variety of optical malformations suggests that it should be possible to test this hypothesis with both forward and reverse genetics.

Figuring Out Fats

Basel-Vanagaite et al., page 49

By now, we all know that a high fat diet increases the likelihood of developing numerous health problems, including obesity and coronary artery disease. For some people, however, elevated triglyceride levels are caused by genetics, not fast food. Unfortunately, the causes of hereditary hyperglyceridemia are known in less than 5% of cases. In this issue, Basel-Vanagaite et al. identify homozygous splice-site mutations in glycerol-3 phosphate dehydrogenase (*GPD1)* in a rare form of hypertriglyceridemia that affects infants and predisposes them to cirrhosis. GPD1 is an enzyme with a known role in glycerol metabolism, but to date, defects in its function have not been implicated in human disease. Specifically, GPD1 is required for the transportation of reducing equivalents from the cytoplasm to the mitochondria. Expression of this mutant version of *GPD1* increased triglyceride secretion in cultured cells, thus providing a launching pad for future mechanistic studies and clinical interventions. Although the hyperglyceridemia is transient in this disorder, tackling the elevated triglycerides early on could prevent several related health problems that develop later in life—although they still might want to steer clear of hamburgers and fries.

Uncovering a Signaling Web

Mitchell et al., page 69
and Kalay et al., page 76

Pterygium sydromes comprise a group of congenital disorders typified by skin webs and craniofacial anomalies. Although causative mutations have been identified for some of these disorders, the underlying genetic cause of Bartsocas-Papas syndrome remained elusive because of early lethality in affected individuals. Through homozygosity mapping and exome sequencing, Kalay et al. and Mitchell et al., respectively, have uncovered mutations that cause this disorder and in so doing have increased our understanding of basic skin biology. Both groups identified heterozygous *RIPK4* mutations in affected individuals. A kinase that activates the NF-κB and JNK pathways, RIPK4 was known to play a role in keratinocyte differentiation, but questions remained regarding its regulation. Satisfyingly, Mitchell et al. gained additional insight into the mechanism by which RIPK4 influences skin development by showing that ΔNp63α, a master regulator of epithelial development, directly regulates *RIPK4* transcription. ΔNp63α also activates *IRF6* and *IKKA*, genes mutated in related disorders, pointing to the existence of a nodal point in the genesis of an even wider range of pterygium syndromes. These studies therefore provide crucial information to clinicians, but also should attract the attention of basic biologists studying skin development and inflammatory responses.

X Marks the Spot

Lederer et al., page 119

Long recognized as enforcing an extra layer of gene regulation, altered histone modifications have been implicated in mediating several key developmental processes. Not surprisingly, then, several enzymes involved in the deposition and removal of histone modifications have

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been implicated in tumorigenesis and cancer progression. How the placement of these marks translates to other human diseases, however, is just starting to be appreciated. Mutations in *MLL2*, which encodes a histone methyltransferase, cause over half of the cases of Kabuki syndrome, typified by developmental delay and diverse congential anomalies. In this issue, Lederer et al. show that microdeletions encompassing *KDM6A*, a gene located on the X chromosome, can also cause Kabuki syndrome. KDM6A demethylates mono-, di-, and tri-methylated histone H3K27, events implicated in diverse developmental processes. Interestingly, MLL2 and KDM6A are interaction partners, pointing to the possibility that although Kabuki syndrome is a genetically heterogeneous disorder, a single disrupted cellular pathway might be to blame. Overall, these findings highlight the increasingly appreciated importance of histone methylation/demethylation in intellectual disability syndromes, and suggest that genes encoding related enzymes might be good candidates for future sequencing studies in this family of disorders. Moreover, given that cancer is not a characteristic feature of Kabuki syndrome, the described roles of *MLL2* and *KDM6A* as tumor suppressors suggests that we really are only just beginning to understand the complex nature of histone modifications in human disease.

Another Piece in the ASD Puzzle

Vaags et al., page 133

With nearly 1 in 110 children affected by autism spectrum disorder (ASD), the race is on to identify and understand the underlying genetic factors. Indeed, de novo and rare inherited CNVs, along with point mutations, have been identified in several genes. However, the picture is far from complete, as one might expect from such a complex group of disorders. In this issue, Vaags and colleagues find rare, inherited microdeletions at the NRXN3 locus. Interestingly, the nature of the deletion seems to correlate with the severity of ASD phenotypes. Specifically, this locus encodes two *NRXN3* isoforms, and individuals harboring deletions affecting both isoforms display more severe forms of ASD. Additionally, the authors' sequencing efforts identified several missense mutations (in different genes) which could represent potential modifiers. NRXN3 belongs to the neurexin family, a group of proteins known to perform important functions in the brain. Previous studies have pointed to a role for *NRXN1* and *NRXN2* alterations in ASD, and so these latest findings highlight that this pathway, when dysregulated, can lead to ASD. Although the work is far from over, this latest report provides important insights on the biology of these disorders which affect an ever-increasing number of families.